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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

INDACATEROL ACETATE-GLYCOPYRRONIUM BROMIDE-MOMETASONE FUROATE (ENERZAIR BREEZHALER)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Asthma maintenance, adults

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CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
AQLQ	Asthma Quality of Life Questionnaire
BIA	budget impact analysis
COPD	chronic obstructive pulmonary disease
ED	emergency department
EQ-5D	EuroQol 5-Dimensions
GINA	Global Initiative for Asthma
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroid
LABA	long-acting beta2 agonist
LAMA	long-acting muscarinic agonist
OCS	oral corticosteroid
QALY	quality-adjusted life-years
QoL	quality of life
QVM	indacaterol acetate-glycopyrronium bromide-mometasone furoate
SABA	short-acting beta2 agonist
SF	salmeterol-fluticasone propionate
TIO	tiotropium

Executive Summary

The executive summary is comprised of 2 tables (Table 1: Submitted for Review; Table 2: Summary of Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Indacaterol acetate-glycopyrronium bromide-mometasone furoate (QVM; Enerzair Breezhaler; 150 mcg indacaterol acetate, 50 mcg glycopyrronium bromide, and 160 mcg mometasone furoate), inhalation powder hard capsules, delivered via the Breezhaler device
Submitted price	QVM: $3.43 per capsule
Indication	Maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta2 agonist and a medium or high dose of an inhaled corticosteroid who experienced 1 or more asthma exacerbations in the previous 12 months
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	July 2, 2020
Reimbursement request	As per indication
Sponsor	Novartis Pharmaceuticals Canada Inc.
Submission history	Not previously reviewed

NOC = Notice of Compliance; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis
Target population	Adults not adequately controlled with a maintenance combination of a LABA and a medium or high dose of an ICS who experienced 1 or more asthma exacerbations in the previous 12 months
Treatment	QVM
Comparator	SF (50 mcg salmeterol and 500 mcg fluticasone propionate) + 5 mcg TIO
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs, asthma exacerbations (severe, moderate)
Time horizon	Lifetime (50 years)
Key data source	ARGON trial
Submitted results for base case	QVM was less costly and more effective (dominant) compared with SF + TIO (cost savings = $17,406, incremental QALYs = 0.31)
Key limitations	• Uncertainty exists regarding the cost-effectiveness of QVM relative to other ICS-LABA + LAMA treatments. Due to a lack of comparative evidence, only 1 of several currently available ICS-LABA treatments was considered in the sponsor's submission. • The price of SF was based on the brand-name version, despite the availability of a generic. • Health utility estimates were based on end-of-trial data, measured by use of a non–preference-based asthma quality-of-life instrument. Quality-of-life estimates were mapped to the EQ-5D, and it is unclear if the preferences reflect those of Canadian patients. • The impact of adverse events on the cost-effectiveness estimate is uncertain, as adverse events were not considered in the sponsor's model. Adverse events were commonly experienced by participants in both treatment groups in the ARGON trial.

Component	Description
	• There is limited evidence on the duration of the treatment effect. The sponsor assumed 50 years of treatment effect on the basis of a 24-week trial.
CADTH reanalysis results	In the CADTH reanalysis, the price of SF was corrected and utility values were assumed to be equivalent across treatments. CADTH was unable to address the cost-effectiveness relative to other ICS-LABA + LAMA treatments due to uncertainty associated with the long-term clinical effectiveness and the impact of adverse events on the ICER. • Based on CADTH reanalyses, QVM remained less costly and more effective than SF + TIO (cost savings = $6,674, incremental QALYs = 0.0085).

ICER = incremental cost-effectiveness ratio; ICS = inhaled corticosteroids; LABA = long-acting beta2 agonist; LAMA = long-acting muscarinic antagonist; LY = life-year; QALY = quality-adjusted life-year; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SF = salmeterol-fluticasone propionate; TIO = tiotropium bromide.

Conclusions

CADTH undertook reanalyses to address limitations in the sponsor's submission, including correcting the price of the inhaled corticosteroid (ICS) plus long-acting beta2 agonist (LABA) price and assuming no difference in health state utility values between treatments. The results of CADTH's analyses were consistent with those submitted by the sponsor. In the CADTH base case, indacaterol acetate-glycopyrronium bromide-mometasone furoate (QVM) was as effective and less costly than salmeterol-fluticasone propionate (SF) + tiotropium (TIO; cost savings = $6,674, incremental quality-adjusted life-years [QALYs] = 0.0085).

CADTH was unable to address the cost-effectiveness of QVM relative to other currently available ICS-LABA + long-acting muscarinic antagonist (LAMA) treatments, the impact of adverse events (AEs) on the cost-effectiveness estimate, and duration of treatment effect beyond the duration of the clinical trials. However, QVM is the least expensive treatment option available to asthma patients who require a medium- or high-dose ICS-LABA + LAMA combination. Where QVM is considered as safe and effective as other ICS-LABA + LAMA alternatives, then it is likely cost-effective. Alternatively, where QVM is viewed to be less effective or associated with greater harms than current treatment options, the cost-effectiveness of QVM would need to be assessed.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process.

Patient input was received from the Lung Health Foundation and Asthma Canada in response to the joint call by CADTH for patient input into the reviews of indacaterol acetate-mometasone furoate (Atectura Breezhaler) and QVM (Enerzair Breezhaler). These patient groups provided input intended for use in both reviews. The Lung Health Foundation gathered information via interviews with 3 patients with asthma (May 2020), while Asthma Canada gathered information through interviews and an online survey involving 24 and 200 patients with asthma, respectively, as part of a 2014 report.[1] Asthma Canada conducted an additional online survey in 2020 (192 respondents) to provide additional information for the current evidence submission.

Both patient groups described the challenges associated with asthma, including wheezing, coughing, shortness of breath, a tight sensation in the chest, fatigue, and difficulty fighting colds and infections. Such symptoms occur in a chronic manner and also as acute severe attacks (exacerbations). Patients also described how asthma limits their daily activities and exercise, as well as how it affects their performance at work or school and causes missed days of school or work. Patients described visits to the emergency department (ED) because of asthma, with many respondents having more than 1 ED visit and/or hospital admission in the previous year because of their asthma.

Both patient groups expressed a desire for improved quality of life (QoL) and lung function. Key outcomes that patients would like addressed include a reduction in shortness of breath, coughing, and fatigue, as well as an improved ability to control day-to-day symptoms, an improved ability to exercise (higher energy level), and an increased ability to fight colds and infections.

Asthma Canada reported that asthma management in current Canadian clinical practice involves the avoidance of triggers that worsen symptoms, the use of a long-term controller medication on an ongoing basis, and the use of a short-acting reliever medication for exacerbations or severe symptoms. Patients reported treatment experience with Symbicort, Ventolin, Advair, Spiriva, Prednisone, and Singular, which provided some relief for their symptoms. Reported side effects of medications experienced by patients include dry mouth or thrush, hoarseness, appetite loss, impact on mood, difficulty sleeping, increased heart rate, and “feeling jittery/shaky.”

Patients emphasized the need to make trade-offs between side effects and asthma control. For patients with severe asthma, side effects may regularly disrupt their activity levels, including social and work interactions, and can lead to a lower health-related QoL. When evaluating a new medication, patients described considering how the medication is administered, the side effects, and the financial burden. In terms of administration, patients agreed that being able to combine medications into 1 device safely would be beneficial. Based on the results of the 2014 Asthma Canada survey,[1] more than half of respondents do not regularly take their long-term controller medication, and Asthma Canada reported that patients often believe they that do not need to continue taking their medications when they are asymptomatic. Other reasons for non-compliance include lack of efficacy (continued exacerbations), side effects, and financial burden.

Several of these aspects were addressed in the sponsor's model:

- The clinical effectiveness of asthma treatments was based on the rate of asthma exacerbations (moderate, severe). Those who experienced a severe exacerbation were assumed to have a lower health-related QoL for 4 weeks. The sponsor assumed that moderate exacerbations would not affect patients' QoL.
- Loss of workplace productivity due to absenteeism was considered via scenario analyses.

Some aspects were not directly addressed in the sponsor's model and could not be addressed by CADTH owing to structural or data limitations:

- AEs related to asthma treatment
- Treatment compliance and adherence
- Improvements in lung function, although this may have been captured as part of QoL measures.

Economic Review

The current review is for QVM (Enerzair Breezhaler) once-daily maintenance treatment of asthma and reduction of asthma exacerbations in adults not adequately controlled with a maintenance combination of a LABA and an ICS.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis assessing QVM, a once-daily fixed-dose combination inhaler including an ICS (mometasone furoate), LABA (indacaterol acetate), and LAMA (glycopyrronium bromide), in patients with asthma not adequately controlled on a maintenance ICS-LABA combination treatment.[2] Treatment with QVM is indicated as a maintenance therapy for asthma in adult patients not adequately controlled with a maintenance combination of a LABA and a medium or high dose of an ICS who experienced 1 or more asthma exacerbations in the previous 12 months.[3] The sponsor's base-case analysis was based on the ARGON clinical trial and was aligned with the funding request. No subgroup analyses were performed.

One strength of QVM (150 mcg indacaterol acetate, 50 mcg glycopyrronium bromide, and 160 mcg mometasone furoate) is approved by Health Canada, and the recommended dosage is 1 capsule once daily. The sponsor's analysis compared QVM to high-dose SF (Advair Diskus; 50 mcg salmeterol and 500 mcg fluticasone propionate), an ICS-LABA fixed-dose combination administered with an inhaler twice daily in addition to TIO (Spiriva Respimat; 5 mcg), and a separate LAMA inhaler once daily (SF + TIO). The annual drug cost of QVM is $1,251 per patient based on a unit cost of $3.43 per capsule.

The clinical outcomes were QALYs, life-years, and number of asthma exacerbations (severe, moderate, and total). The sponsor adopted a lifetime horizon (50 years) using 4-week cycles and undertook the analysis from the perspective of the publicly funded health care payer. Costs and clinical outcomes were discounted at a rate of 1.5% per year.

Model Structure

The economic analysis was conducted using a Markov model in Microsoft Excel. The model consisted of 2 health states: day-to-day symptoms and death (the absorbing health state) (Appendix 3). Patients in the day-to-day symptoms state could experience moderate or severe exacerbations. For patients who experience a severe exacerbation, 5% were assumed to require admission to hospital, while 5% were assumed to visit an ED (but not be admitted to hospital) and 90% were assumed to manage their exacerbation with an oral corticosteroid (OCS) burst. Severe exacerbations were further assumed to require treatment with prednisone (for 5 days if the patient required an OCS burst or ED visit, 30 days if admitted to hospital). Moderate exacerbations were managed with 3 days of prednisone treatment.

Model Inputs

The baseline patient characteristics in the sponsor's model were aligned with the ARGON trial, a phase III, multi-centre, randomized, non-inferiority, active-controlled trial.[4] The ARGON trial compared 2 doses of QVM (150 mcg indacaterol acetate, 50 mcg glycopyrronium bromide, and 160 mcg mometasone furoate [150 mcg/50 mcg/160 mcg] and 150 mcg indacaterol acetate, 50 mcg glycopyrronium bromide, and 80 mcg mometasone furoate [150 mcg/50 mcg/80 mcg]) to SF + TIO over a 24-week treatment period. Treatment with QVM 150 mcg/50 mcg/80 mcg is not approved by Health Canada and was subsequently removed from the submission. Participants in the ARGON trial were at least 18 years old with a diagnosis of asthma (a pre-bronchodilator forced expiratory volume in 1 second of less than 85% of the predicted normal value, symptomatic despite treatment with medium or high stable doses of an ICS-LABA, a 7-item Asthma Control Questionnaire score of least 1.5, and 1 or more severe asthma exacerbations in the previous 12 months). Patients with a history of smoking at least 20 pack-years and those with chronic obstructive pulmonary disease (COPD) were excluded. The mean participant age in the ARGON trial was 53 years, and 63% of participants were female.

The clinical efficacy of QVM, as well as the comparator (SF + TIO), in terms of asthma exacerbations was obtained from the ARGON trial. Severe exacerbations in the ARGON trial were defined as aggravation of asthma symptoms that required systemic corticosteroids for at least 3 consecutive days and/or a need for an ED visit, hospitalization due to asthma, or death due to asthma. In the pharmacoeconomic submission, the rate of severe exacerbations was incorporated directly from the ARGON trial, and the rate of moderate exacerbations was calculated by subtracting the rate of severe exacerbations observed in the ARGON trial from the rate of all exacerbations for each treatment. Treatment effect was assumed to be maintained over the model time horizon. Mortality among patients with asthma was assumed to be equivalent to the Statistics Canada age- and gender-specific general population mortality rates. No AEs were included in the sponsor's economic evaluation, and discontinuation from treatment was not included in the sponsor's base-case analysis.

Health state utility values for the day-to-day symptom state were derived from the Asthma Quality of Life Questionnaire (AQLQ) estimates from the ARGON trial. The AQLQ is a 32-item asthma-specific questionnaire that measures function across 4 domains (symptoms, activity limitation, emotional function, environmental stimuli), with a summary score of the mean response to all 32 items. Total AQLQ scores after 24 weeks of treatment were mapped onto the EuroQol 5-Dimensions (EQ-5D) questionnaire by use of a mapping function. Disutilities related to exacerbations that required either hospital admission or an

OCS burst were obtained from a 2007 study involving 112 patients in the UK with moderate-to-severe asthma, in which disutility values were based on a subset of 5 patients who were hospitalized (for hospitalization disutility) or 22 patients who required an OCS burst.[5] The sponsor assumed that disutility related to ED visits would be equal to that associated with an OCS burst. Disutilities were assumed to be experienced for the full duration of one 4-week model cycle in which an exacerbation occurred.

The economic model included drug costs, as well as exacerbation-related costs to the health care system (i.e., unscheduled visits to a general practitioner, ED visits, general hospital ward visits, general hospital outpatient visits, nurse educator expenses, and days of prednisone use). The drug price of QVM was obtained from the sponsor, and the prices of SF and TIO were obtained from the Ontario Drug Benefit Formulary.[6] The sponsor based the price of SF on the Ontario Drug Benefit list price for the brand-name SF dual therapy (Advair Diskus). Exacerbation-related use of health care resources was based on clinical expert opinion, and costs were obtained from the Ontario Schedule of Benefits for Physician Services[7] and the Ontario Case Costing Initiative[8] for physician and hospital admission and/or ED visit costs, respectively. All costs were presented in 2020 CA$, and costs obtained from other years were inflated to 2020 CA$.

Summary of Sponsor's Economic Evaluation Results

The sponsor's cost-effectiveness analysis was based on 1,000 probabilistic iterations, for which findings are presented below. Additional details pertaining to the sponsor's submission are available in Appendix 3.

Base-Case Results

In the sponsor's base-case analysis, QVM was associated with an expected cost of $33,501 and 18.37 QALYs over a 50-year horizon (Table 3). Treatment with QVM produced more QALYs and was less costly compared to SF + TIO. At a willingness-to-pay threshold of $50,000 per QALY, QVM had an 85.8% probability of being cost-effective.

Additional results from the sponsor's submitted economic evaluation base case are presented in Appendix 3.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. SF + TIO ($ per QALY)
QVM	33,501	–	18.37	–	–
SF + TIO	50,907	17,406	18.06	−0.31	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SF = salmeterol-fluticasone propionate; TIO = tiotropium; vs. = versus.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments.

Source: Sponsor's pharmacoeconomic submission.[2]

Sensitivity and Scenario Analysis Results

The sponsor conducted several sensitivity and scenario analyses. These included adopting a societal perspective (including productivity costs), varying the time horizon (to 10 years), varying the discount rate (0% and 3%), and including treatment discontinuation. In all scenarios, QVM remained the most cost-effective option, at a $50,000 willingness-to-pay threshold.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Appropriate comparators were omitted.** The sponsor's pharmacoeconomic submission compared the cost-effectiveness of QVM plus SF + TIO. As an ICS-LABA combination treatment, SF is one of several ICS-LABAs currently authorized in Canada (Table 7). A network meta-analysis to compare ICS-LABA treatments was deemed not feasible due to heterogeneity in terms of study population, study treatment duration, and outcome definitions, as well as a lack of common comparators. The sponsor's submission was therefore based on direct evidence comparing QVM with SF + TIO from the ARGON trial.
- One additional ICS-LABA + LAMA fixed-dose combination treatment is available in Canada (Trelegy Ellipta; fluticasone furoate-umeclidinium-vilanterol). Trelegy Ellipta is indicated for the treatment of COPD; however, the clinical expert consulted by CADTH noted that it may be prescribed to approximately 5% to 10% of patients with asthma.
  - The clinical effectiveness and cost-effectiveness of QVM relative to most currently available ICS-LABA + LAMA treatments are uncertain. At the submitted price, the annual cost of QVM ($1,251) is less than that of most combination treatments of an ICS-LABA + LAMA (Table 7). The only exception is generic SF at the lowest dose (100 mcg/50 mcg); however, the clinical expert consulted by CADTH indicated that this dose would not typically be prescribed to patients taking an ICS-LABA in combination with a LAMA. The uncertainty of comparator exclusion is dependent on whether it is anticipated that other comparators could be more effective or safer than QVM. Due to the lack of any relevant data, this could not be analyzed by CADTH.
- **Inappropriate comparator price**. In the sponsor's submission, the cost of SF was based on the price of the brand-name drug (Advair Diskus). CADTH deemed that the appropriate comparator price should be based on the generic version of SF.
  - In the reanalysis of the sponsor's submission, as well as in CADTH's base-case and scenario analyses, the generic price of SF was used.
- **Uncertainty regarding differences in health state utility values between treatments.** The sponsor's submitted pharmacoeconomic model incorporated health state utility values for day-to-day asthma symptoms based on the end-of-treatment assessment of asthma-specific QoL as measured by the AQLQ questionnaire in the ARGON trial. The AQLQ is a non–preference-based assessment measure, and the sponsor mapped AQLQ estimates to the EQ-5D using a mapping function.[9] The mapping approach was not well described, and the paper cited by the sponsor for the mapping function is not available in a peer-reviewed journal (i.e., it is a non–peer-reviewed discussion paper only). This discussion paper describes multiple methods of mapping AQLQ to EQ-5D, and CADTH could not verify which approach was taken by the sponsor.

  The ARGON study was a multinational trial with no Canadian sites. The mapping function used by the sponsor to convert AQLQ estimates to utility values is based on preference weights from the UK population–based study.[9] Weighting of EQ-5D health states varies by country,[10] and utilities weighted for Canadian preferences should be used for economic evaluations based in Canada.[11] It is therefore unclear whether the utilities incorporated in the sponsor's submission are reflective of Canadian preferences.

  The utility values included in the sponsor's submission from both trials were based on end-of-treatment data, which were gathered over 24 weeks in the ARGON trial. The sponsor assumed that the effect of treatment on QoL would be permanent, lasting for the entire 50-year analysis horizon. Further, estimates at this time point reflect participants who completed the trial and do not capture those who withdrew or who did

not complete the assessment. End-of-treatment estimates may therefore be overestimated, as questionnaires may not be missing at random. Further, the upper and lower limits of the distribution of health utility values included in the sponsor's probabilistic analysis were arbitrarily calculated as ± 5% of the mean value and do not reflect the full range of possible values.

The ARGON trial was open-label with respect to whether the participants were assigned to QVM or SF + TIO (within QVM, assignment to QVM 150 mcg/160 mcg or 150 mcg/320 mcg was blinded). Open-label studies that employ subjective outcome measures (e.g., QoL) are at high risk of bias, and may overestimate the treatment effect.[12]

- It is uncertain whether there is a utility benefit associated with QVM, whether it is maintained past the end of the trial period, and whether the utilities reflect the preferences of Canadian patients. In CADTH's reanalysis, equal utility values were attributed to both treatments.

- **Impact of AEs is uncertain.** The pharmacoeconomic analysis submitted by the sponsor did not incorporate costs to the health care system or decreased participant QoL as a result of AEs, which may affect total costs and QALYs. The sponsor's submission stated that this was due to the low incidence of AEs and the potential impact on the analysis. According to the clinical expert consulted by CADTH, assuming a low incidence of AEs is unreasonable, particularly for high-dose ICS treatments.[13] The long-term use of high doses of ICS is associated with AEs, including pharyngitis, dysphonia, reflex coughing, bronchospasms, oropharyngeal candidiasis, suppressed hypothalamic-pituitary-adrenal axis function, adrenal crisis, reduced bone-mineral density, bone fractures, osteoporosis, skin thinning and bruising, cataracts, and glaucoma.[14]

  As noted in the clinical review, AEs were common in the ARGON trial during the 24-week treatment period, although the percentage of participants who experienced an adverse event was similar between QVM (52.3%) and SF + TIO (51.6%). Serious AEs were reported for [redacted] (SF + TIO) and [redacted] (QVM) of participants. In the stakeholder feedback received from the Lung Health Foundation and Asthma Canada, AEs were of concern to patients, who described how AEs lower health-related QoL. As noted, the ARGON trial was open-label with respect to QVM and SF + TIO, and patient and researcher awareness of treatment allocation may affect evaluations of patient-reported outcomes, including the reporting of AEs.

  - Because the sponsor's submission did not include costs related to treating such AEs or decrements in health-related QoL, the impact of AEs on cost-effectiveness is uncertain. CADTH explored the potential impact of AEs in a scenario analysis.

- **Uncertainty regarding long-term clinical effectiveness.** Participants in the ARGON trial received treatment with QVM or SF + TIO for 24 weeks. In the sponsor's pharmacoeconomic submission, the effects of QVM on asthma exacerbations were considered to be consistent over the 50-year analysis horizon, and the potential waning of the treatment effect over time was not considered. The clinical expert consulted by CADTH indicated that the clinical effectiveness of asthma therapies should be evaluated over at least 1 year in clinical trials to capture seasonal variation in exacerbations.

  - It is uncertain whether the effect of QVM on asthma exacerbations is maintained beyond the duration of treatment in the ARGON trial.

Additional limitations were identified but were not considered to be key limitations:

- **Overestimation of clinical benefit.** Clinical effectiveness in the sponsor's submission was characterized by the rate of moderate and severe asthma exacerbations, which the sponsor states was based on data from the ARGON trial. CADTH identified several discrepancies between the exacerbation rates in the pharmacoeconomic submission[2] and the clinical study report for the ARGON trial.[4] For example, in the ARGON trial, the rate of total exacerbations includes mild, moderate, and severe exacerbations. In the

pharmacoeconomic submission the sponsor calculated the rate of moderate exacerbations by subtracting the severe rate from the total rate (i.e., without accounting for mild exacerbations). As a result, the value included in the model for moderate exacerbation includes mild exacerbations, thus overestimating the number of moderate exacerbations averted. This discrepancy affects QVM as well as SF + TIO and would not be expected to substantially affect costs or QALYs because moderate exacerbations were associated with minor costs and no disutility.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Patients were assumed to stay on the same dose and formulation for their lifetime.	Unreasonable. The clinical expert consulted by CADTH, as well as the GINA guidelines,[15] indicated that treatment response should be periodically reviewed and treatment dose reassessed in light of the patient's response in terms of symptom control and risk of future exacerbations and side effects. Once good asthma control has been achieved, treatment may be stepped down to find the minimum treatment dose that controls both symptoms and exacerbations. Further, the clinical expert consulted by CADTH indicated that patients with suboptimal asthma control may be interested in trying new drug formulations as they become available.
Patients with asthma were considered to be at minimal risk of increased mortality compared to the general population.	Reasonable. The clinical expert consulted by CADTH indicated that this assumption was reasonable. Further, as there was no observed difference in mortality between QVM and the comparator treatments in the clinical trials, any difference in overall mortality would be expected to have a minimal effect on the ICER. The GINA guidelines note, however, that the risk of asthma-related death may be increased by admission to hospital or ED visits in the past year, as well as by poor adherence to asthma medications.[15]
Resource utilization was based on medical expert opinion.	Uncertain. The resource utilization estimates incorporated into the sponsor's submission were based on the sponsor's consultation with a Canadian medical estimate. The clinical expert consulted by CADTH indicated that these estimates were not in keeping with current Canadian clinical practice. Particularly, the sponsor assumed that patients admitted to hospital for a severe exacerbation would receive 30 days of prednisone treatment, whereas current Canadian practice is up to 10 days. Further, the sponsor assumed that admission to hospital would not be associated with an ED visit, which is not in keeping with current practice.
The duration of disutility (i.e., lower health-related quality of life) associated with severe asthma exacerbations was assumed to be equal to the cycle length (4 weeks).	Reasonable. The clinical expert consulted by CADTH indicated that patients may experience decrements in health for 4 to 6 weeks following a severe asthma exacerbation.
For patients with a severe exacerbation, 90% would require an OCS burst, 5% would visit an ED, and 5% would be admitted to hospital.	Uncertain. The clinical expert consulted by CADTH indicated that patients with asthma are rarely admitted to hospital in Canada, and that contemporary Canadian data would be required to verify this assumption. The sponsor's assumptions were based on non-Canadian studies from 2005 to 2015.[16-18]
Moderate exacerbations would be treated with prednisone for 3 days only (i.e., no additional costs related to health care resource use).	Uncertain. The clinical expert consulted by CADTH indicated that patients would likely receive 5 days of prednisone (50 mg per day), and the GINA guidelines state that short-course OCS treatment may last up to 7 days (40 mg per day to 50 mg per day). Patients may require a visit to a health care provider to obtain an OCS prescription if no asthma action plan is in place. The clinical expert indicated that approximately 20% to 30% of patients may have such a plan. For the

Sponsor's key assumption	CADTH comment
	remaining patients, a visit or call with a health care provider would be required to obtain a prednisone prescription. GINA guidelines further recommend that patients who self-manage an exacerbation should see their health care provider to review their symptom control and risk factors for exacerbations, and to identify potential causes of the exacerbation.[15] Patients who experience more than 1 to 2 exacerbations per year despite step 4 and 5 therapy should be referred to a specialist centre for assessment.

ICER = incremental cost-effectiveness ratio; ED = emergency department; GINA = Global Initiative for Asthma; OCS = oral corticosteroid; QVM indacaterol acetate-glycopyrronium bromide-mometasone furoate.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH reanalyses addressed several limitations within the economic model and the results are summarized in Table 5. Due to structural and/or data limitations, CADTH was unable to address the cost-effectiveness of QVM relative to other currently available ICS-LABA + LABA treatments, the impact of AEs, and the duration of treatment effect.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
Corrected SF cost calculation	Cost of SF was based on the brand-name product	Cost of SF was based on the generic product
Changes to derive the CADTH base case		
Assumed no difference in utilities across treatments	Utilities were based on end-of-treatment non–preference-based QoL assessment, mapped to the EQ-5D	No difference in utilities across treatments
CADTH base case	–	Reanalysis 1

EQ-5D = EuroQol 5-Dimensions; QoL = quality of life; SF = salmeterol-fluticasone propionate.

CADTH's base-case results are presented in Table 6.

In CADTH's base case, QVM was associated with lower costs compared with SF + TIO (incremental: −$6,674) and higher QALYs (incremental: 0.01) over a 50-year time horizon, thus dominating SF + TIO (QVM was less costly and more effective). At a willingness-to-pay threshold of $50,000 per QALY, 57% of simulations resulted in QVM being cost-effective. It should be noted that in 50% of iterations QVM was associated with poorer health outcomes, therefore QMV's lower drug cost is driving the cost-effectiveness result. The disaggregated results are presented in Table 11 in Appendix 4.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($ per QALY)
Sponsor's base case	QVM[a]	33,501	18.37	–
	SF + TIO	50,907	18.06	Dominated
Sponsor's corrected base case	QVM	33,510	18.3739	–
	SF + TIO	40,184	18.0583	Dominated
CADTH reanalysis 1	QVM	33,506	18.0685	–
	SF + TIO	40,180	18.0600	Dominated
CADTH base case (reanalysis 1)	QVM	33,506	18.0685	–
	SF + TIO	40,180	18.0600	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SF = salmeterol-fluticasone propionate; TIO = tiotropium.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

[a] Reference product is the least costly alternative.

Scenario Analysis Results

Scenario analyses were conducted using the CADTH base case to investigate the impact of an alternative ICS-LABA comparator dose and an alternative proportion of patients admitted to hospital for severe asthma exacerbations (Table 12).

In the CADTH scenario analyses, assuming a lower ICS-LABA dose had a minimal effect on the cost-effectiveness estimate (QVM remained dominant) (Table 13). Reducing the proportion of patients admitted to hospital resulted in slightly higher QALYs with SF + TIO (18.074) relative to QVM (18.068) and an incremental cost-effectiveness ratio of $1,190,493 for SF + TIO (versus QVM).

To explore the potential impact of utility differences between treatments, CADTH reduced the utility value associated with QVM by 0.01. In this scenario, QVM was no longer a cost-effective treatment option. While QVM remained less costly than SF + TIO, these savings did not compensate for the reduction in utility. This scenario analysis emphasizes the need for QVM to be as effective and safe as current treatment options for it to be cost-effective.

As evidence regarding QVM's superiority over other comparators is uncertain, QVM should be priced no more than the least expensive ICS-LABA + LAMA combination therapy. Because QVM is less expensive than all other medium- to high-dose ICS-LABA combination therapies used with a LAMA, no price reduction analysis was conducted. Because single ICS inhalers plus single LABA inhalers are infrequently used and are more expensive than their combination counterparts, they are not relevant in the price comparison.

Issues for Consideration

- Participants in the ARGON trial may not be reflective of the Canadian patient population, as the ARGON trial had no Canadian study sites. Further, for inclusion patients were required to have an objective diagnosis of asthma and show reversibility at study entry. In clinical practice, asthma cannot be confirmed in many adults (25% to 35%) who have an asthma diagnosis.[15] Such patients, were they to receive QVM, would not be expected to show an improvement in asthma symptoms. Further, as noted in the clinical review, the study population would likely represent approximately 20% to 30% of patients in clinical practice and the ARGON trial population was potentially enriched by the use of reversibility as an inclusion criterion.

- The sponsor's submission asserts that once-daily treatments may lead to improved compliance relative to twice-daily treatments. Compliance with treatment was not assessed as part of the ARGON trial and was not considered in the sponsor's analysis. Additionally, while there is evidence that adherence may be higher with once-daily versus twice-daily asthma treatments, it is not clear whether this translates to improved patient outcomes.[19] The clinical expert consulted by CADTH indicated that it is unreasonable to assume that patients will be 100% adherent to their prescribed treatment. The clinical expert consulted by CADTH indicated that adherence may depend, in part, on ease of use of the inhaler device. Breezhaler, the delivery device for QVM, was not considered by the clinical expert to be easy to use relative to other available inhaler devices. Further, as described in the clinical review, the Breezhaler device is perceived by patients as being more difficult to use compared with other inhalation devices, and errors are more common with Breezhaler than with other devices, which may affect patient adherence, clinical effectiveness, and medication costs associated with QVM.

Overall Conclusions

In the sponsor's base-case analysis, QVM was more effective and less costly than SF + TIO. The results of CADTH's reanalyses, which addressed limitations, such as correcting the price of SF and assuming no difference in health state utility values across treatments, were consistent with the sponsor's analysis. In this scenario, no price reduction would be required to ensure that QVM is cost-effective.

CADTH's reanalysis could not address several important limitations. Notably, the long-term clinical effectiveness and AE profile of QVM relative to other currently available comparators are unclear. Many ICS-LABA treatments are available in Canada for maintenance treatment of asthma, and while QVM is less costly than most, the per-patient saving is relatively small and would only be justified if QVM provides the same health outcomes. CADTH tested this assumption in an exploratory analysis, in which a small reduction in utility related to day-to-day symptoms would result in an incremental cost-effectiveness ratio greater than $50,000 per QALY.

Thus, the cost-effectiveness findings hold only if the comparative clinical effects and AE profile of QVM are similar to those for SF + TIO and other currently available ICS-LABA + LAMA treatments. If the assumptions do not hold, the cost-effectiveness of QVM is unknown.

Appendix 1: Cost Comparison Table

The comparators presented in Table 7 have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Costs of comparator products were sourced from the Ontario Drug Benefit Formulary[6] (accessed August 2020), unless otherwise specified. Existing product listing agreements are not reflected in the table and, as such, the table may not represent the actual costs to public drug plans.

Table 7: CADTH Cost Comparison for Maintenance Regimens for Asthma – ICS-LABA Fixed-Dose Combination Treatments and ICS-LABA + LAMA Combination Treatments

Treatment	Strength	Form	Price ($)	Recommended dosage		Daily cost ($)	Annual cost[a] ($)
QVM (Enerzair Breezhaler)	**150 mcg/50 mcg/160 mcg**	**Inhalation powder hard capsules (30 doses)**	**102.82**	**1 capsule inhaled daily**		**3.43**	**1,251**
LAMA							
TIO (Spiriva Respimat)	2.5 mcg	Soft mist inhaler (60 doses)	54.2607	2 inhalations once daily		1.81	660
ICS-LABA fixed-dose combinations + LAMA							
Budesonide-formoterol fumarate dihydrate (Symbicort Turbuhaler) + TIO (Spiriva Respimat)	Budesonide-formoterol fumarate dihydrate: 100 mcg/6 mcg and 200 mcg/6 mcg	Inhalation powder (120 doses)	69.5400 90.3600	Low	100 mcg/6 mcg, 2 inhalations twice daily	2.32	Low: 1,506 Medium: 1,759 High: 2,859
				Medium	200 mcg/6 mcg, 4 inhalations daily	3.01	
				High	200 mcg/6 mcg, > 4 inhalations daily[c]	6.02	
	TIO: 2.5 mcg	Soft mist inhaler (60 doses)	54.2607	2 inhalations once daily		+1.81	
SF (Advair) + TIO (Spiriva Respimat)	SF: 25 mcg/ 125 mcg and 25 mcg/250 mcg	MDI (120 doses)	105.0700 149.1600	Low	125 mcg/25 mcg, 1 inhalation twice daily	1.75	Low: 1,299 Medium: 1,939 High: 2,475
				Medium	125 mcg/25 mcg, 2 inhalations twice daily	3.50	
				High	250 mcg/25 mcg, 2 inhalations twice daily	4.97	
	TIO: 2.5 mcg	Soft mist inhaler (60 doses)	54.2607	2 inhalations once daily		+1.81	
SF (Advair Diskus, generic) + TIO (Spiriva Respimat)	SF: 50 mcg/ 100 mcg, 50 mcg/250 mcg,	Inhalation powder (60 doses)	42.4050 50.7600 72.0600	Low	100 mcg/50 mcg, 1 inhalation twice daily	1.41	Low: 1,176 Medium: 1,278 High: 1,536
				Medium	250 mcg/50 mcg, 1 inhalation twice daily	1.69	

Treatment	Strength	Form	Price ($)	Recommended dosage		Daily cost ($)	Annual cost[a] ($)
	and 50 mcg/ 500 mcg			High	500 mcg/50 mcg, 1 inhalation twice daily	2.40	
	TIO: 2.5 mcg	Soft mist inhaler (60 doses)	54.2607	2 inhalations once daily		+1.81	
Fluticasone furoate-vilanterol (Breo Ellipta) + TIO (Spiriva Respimat)	Fluticasone furoate-vilanterol: 100 mcg/25 mcg and 200 mcg/25 mcg	Inhalation powder (30 doses)	86.6300 135.6900	Low	NA	NA	Low: NA Medium: 1,714 High: 2,311
				Medium	100 mcg/25 mcg, 1 inhalation once daily	2.89	
				High	200 mcg/25 mcg, 1 inhalation once daily	4.52	
	TIO: 2.5 mcg	Soft mist inhaler (60 doses)	54.2607	2 inhalations once daily		+1.81	
Mometasone furoate-formoterol fumarate dihydrate (Zenhale) + TIO (Spiriva Respimat)	100 mcg/5 mcg and 200 mcg/5 mcg	MDI (120 doses)	97.8600 118.5800	Low	NA	NA	Low: NA Medium: 1,850 High: 2,103
				Medium	100 mcg/5 mcg, 2 inhalations twice daily	3.26	
				High	200 mcg/5 mcg, 2 inhalations twice daily	3.95	
	TIO: 2.5 mcg	Soft mist inhaler (60 doses)	54.2607	2 inhalations once daily		+1.81	

ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; LAMA = long-acting muscarinic antagonist; MDI = multi-dose inhaler; NA = not applicable; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SF = salmeterol-fluticasone propionate.

[a] Annual costs are calculated based on 365 days per year.

Table 8: CADTH Cost Comparison for ICS-LABA/LAMA Treatments Not Specifically Indicated for Maintenance Treatment of Asthma

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)	Annual cost ($)
Fluticasone furoate-umeclidinium bromide-vilanterol trifenatate (Trelegy Ellipta)	100 mcg/62.5 mcg/25 mcg	Inhalation powder (30 doses)	132.2000	1 inhalation daily[b]	4.41	1,608

[a] Annual costs are calculated based on 365 days per year.

[b] Based on clinical expert input.

Appendix 2: Submission Quality

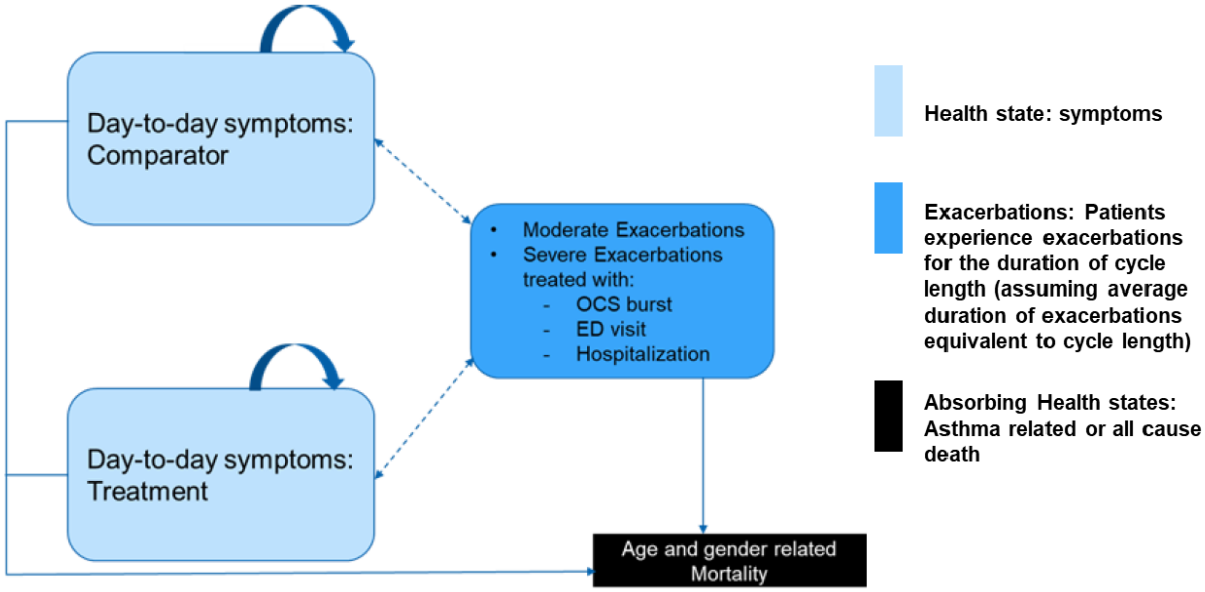
Table 9: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing.	☐	☒	The sponsor's analyses considered only 1 of several currently available ICS-LABA comparator treatments. The participants in the clinical trials may not reflect those seen in clinical practice in Canada.
Model has been adequately programmed and has sufficient face validity.	☒	☐	
Model structure is adequate for decision problem.	☒	☐	The sponsor's analysis does not account for AEs; AEs were identified as being of concern to patients and may be associated with additional costs to the health care system. The risk of AEs may be higher at high ICS doses.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis).	☒	☐	The range for utility values was constructed as ± 5% of the mean estimate and does not reflect the full range of possible values.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem.	☒	☐	
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details).	☒	☐	The utility mapping function was not well described.

AE = adverse event; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Model Structure



ED = emergency department; OCS = oral corticosteroid.

Source: Sponsor's pharmacoeconomic submission.[2]

Detailed Results of the Sponsor's Base Case

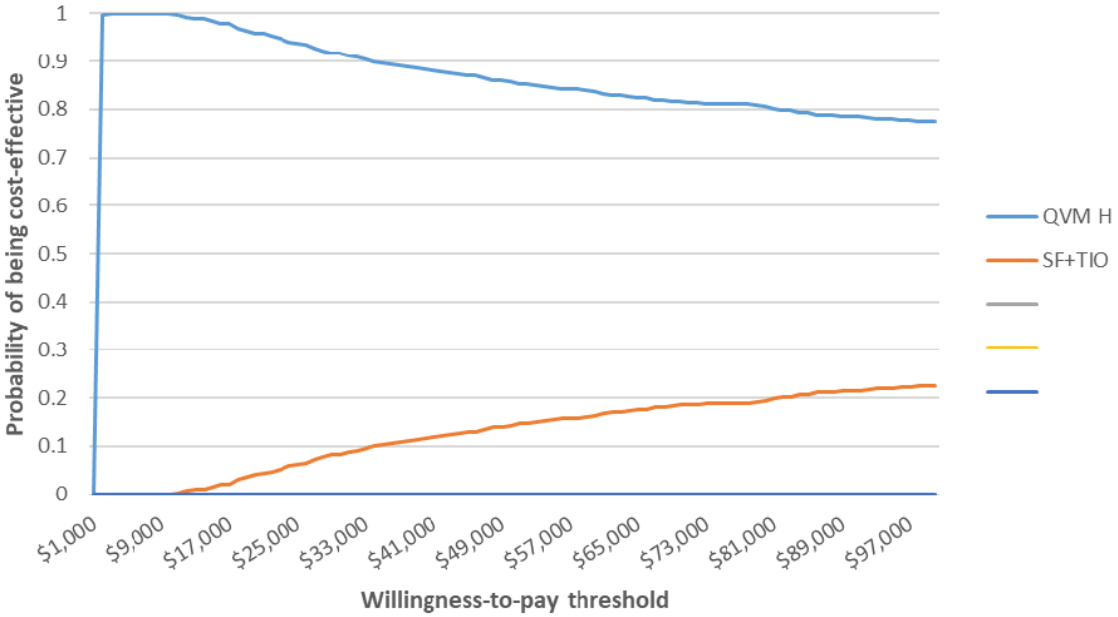
Table 10: Disaggregated Summary of Sponsor's Economic Evaluation Results

Drug	QVM	SF + TIO
Discounted LYs		
Total	24.44	24.44
Discounted exacerbations		
Total (all exacerbations)	17.12	21.01
Moderate exacerbations	8.31	13.17
Severe exacerbations		
Requiring hospitalization	0.44	0.39
Requiring ED visit	0.44	0.39
Requiring OCS burst	7.93	7.06
Discounted costs ($)		
Total	33,501	50,907
Drug costs	30,597	48,313
Exacerbation costs	2,904	2,594

ED = emergency department; LYs = life-years; OCS = oral corticosteroid; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SF = salmeterol-fluticasone propionate; TIO = tiotropium.

Source: Sponsor's pharmacoeconomic submission.[2]

Figure 2: Cost-Effectiveness Acceptability Curve for the Probabilistic Base-Case Analysis



QVM H= indacaterol acetate-glycopyrronium bromide-mometasone furoate high dose; SF = salmeterol-fluticasone propionate; TIO = tiotropium.

Source: Sponsor's pharmacoeconomic submission.[2]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Detailed Results of CADTH Base Case

Table 11: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	QVM	SF + TIO	Incremental
Discounted LYs			
Total	24.44	24.44	0
Discounted QALYs			
Total	18.0685	18.0600	0.0085
Discounted costs ($)			
Total	33,506	40,180	−6,674
Drug	30,598	37,592	−6,994
Exacerbation	2,908	2,589	320
ICER ($ per QALY)	Dominated		

ICER = incremental cost-effectiveness ratio; LY= life-year; QALY = quality-adjusted life-year; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SF = salmeterol-fluticasone propionate; TIO = tiotropium.

Scenario Analyses

Table 12: CADTH Scenario Analyses

	CADTH base case	CADTH scenario
Scenario Analyses		
1. ICS-LABA comparator dose	High-dose ICS-LABA (SF 50 mcg/500 mcg)	Moderate-dose ICS-LABA (SF 50 mcg/250 mcg)
2. Proportion of severe exacerbations that require hospitalization	5%	1%
3. Utility values	No difference in utilities between treatments	Utility value for QVM was decreased by 0.01

ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; SF = salmeterol-fluticasone propionate.

Table 13: CADTH Scenario Analyses Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. SF + TIO ($ per QALY)
Alternative comparator (moderate-dose ICS-LABA + TIO)					
QVM	33,509	–	18.0742	–	–
SF + TIO	33,840	331	18.0505	-0.0237	Dominated
Proportion hospitalized for a severe exacerbation					
QVM	31,896	–	18.0683	–	–
SF + TIO	38,743	6,847	18.0741	0.0058	1,190,493
Alternative utility values					
QVM	33,515	–	17.8072	–	–
SF + TIO	40,181	6,666	18.0631	0.2559	26,051

ICER = incremental cost-effectiveness ratio; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate; QALY = quality-adjusted life-year; SF = salmeterol-fluticasone propionate; TIO = tiotropium; vs. = versus.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Key take-aways of the budget impact analysis

- CADTH identified the following key limitations with the sponsor's analysis:
  - The sponsor assumed that 53% of patients taking an ICS-LABA would remain uncontrolled and be eligible for LAMA treatment. Of these, the sponsor assumed that [redacted] would be taking a concomitant LAMA (ICS-LABA + LAMA) while the remainder would be new users. These assumptions may not reflect the current distribution of Canadian patients with asthma.
  - Assumptions regarding the distribution of claims for asthma relative to other conditions (e.g., COPD) could not be verified, and the proportion of claims attributed to asthma were considered underestimated by the clinical expert consulted by CADTH. Claims were further divided into 2 market segments (medium- and high-dose) for ICS-LABA treatments, and assumptions were required regarding the distribution of claims between segments for some comparator treatments. CADTH was unable to verify the validity of these assumptions.
  - Market uptake of QVM among patients initiating LAMA treatment (in addition to an ICS-LABA; new LAMA users) and among those currently taking an ICS-LABA + LABA was based on the sponsor's internal assumptions. The clinical expert consulted by CADTH indicated that these numbers may be overestimated due to the number of ICS-LABA treatments currently available.
  - CADTH identified several discrepancies between drug prices in the sponsor's submission and costs to the provincial drug plans. The cost of some comparators was therefore overestimated.
  - To calculate population size, the sponsor assumed 100% adherence, which is unlikely to hold true in reality.
- Due to the high degree of uncertainty around these model parameters, CADTH did not reanalyze the sponsor's budget impact analysis (BIA) submission. Given that QVM is less costly than treatments used in current practice, the reimbursement of QVM will likely be cost-saving to drug plans. The extent of these savings is unclear.

Summary of Sponsor's BIA

In the submitted BIA,[20] the sponsor assessed the expected budgetary impact resulting from reimbursing QVM for the maintenance treatment, and to reduce asthma exacerbations, in adults whose asthma is not adequately controlled with a maintenance combination of a LABA and an ICS. The BIA was undertaken from the perspective of the Canadian public payer over a 3-year time horizon (2021 to 2023) using a claims-based approach, and the sponsor's submission considered only drug costs.

The sponsor estimated the number of eligible patients by use of historical drug utilization data from 2016 to 2020. The submitted BIA considered only patients with uncontrolled asthma to be eligible, which was assumed to be 53% of patients taking an ICS-LABA. Two populations were considered: (1) patients with uncontrolled asthma currently taking an ICS-LABA combination therapy plus a concomitant LAMA (concomitant LAMA treatment was considered only for provinces where tiotropium is not restricted to patients with COPD; otherwise, ICS-LABA only), and (2) patients with uncontrolled asthma currently taking an ICS-LABA combination therapy without a concomitant LAMA. The sponsor assumed that 10% of asthmatic patients currently treated with an ICS-LABA also receive a concomitant LAMA.

QVM was compared to currently available ICS-LABA therapies (i.e., budesonide-formoterol fumarate dihydrate [Symbicort Turbuhaler], SF [Advair, Advair Diskus], formoterol fumarate-mometasone furoate [Zenhale], fluticasone furoate-vilanterol [Breo Ellipta]), as well as a concomitant LAMA treatment (i.e., TIO [Spiriva Respimat]). Within each of these populations, the treatments were divided into medium- and high-dose market segments on the basis of recommended daily doses from a previous CADTH pharmacoeconomic

review.[21] Drug costs were based on provincial formularies. For drugs indicated for the treatment of COPD, data from IQVIA Rx Dynamics were used to estimate the percentage of claims for each indication. For drugs or strengths labelled only for asthma, all units were considered to be used in asthma. For drugs that the same dosage can be used in different market segments depending on the number of inhalations per day (i.e., Advair 125, Symbicort 200 mcg/6 mcg), the number of claims was split between market segments based on Advair Diskus (100 mcg/50 mcg and 250 mcg/50 mcg) and Breo Ellipta (100 mcg/25 mcg and 200 mcg/25 mcg). For all comparators, units were transformed into the number of patients by dividing the number of units by the number of units per year based on the dosing schedule.

The market uptake for QVM among patients currently taking an ICS-LABA + LAMA was assumed to be 20% in year 1, then 45% in year 2, and 58% in year 3. For uncontrolled patients currently taking an LABA-ICS only, the market was anticipated at 5% in year 1, then 17% in year 2, and 25% in year 3. Market share for the comparators varied by jurisdiction, and the sponsor assumed that QVM would have the same impact on all currently available treatments (equal displacement).

Deterministic 1-way scenario analyses were conducted to assess the impact of altering the percentage of patients taking a concomitant LAMA (assuming all patients would be new users of an ICS-LABA + LAMA), altering the percentage of patients with uncontrolled asthma, assuming all claims were for the treatment of asthma, and assuming 10% higher or lower uptake of QMV.

Key inputs to the BIA are documented in Table 14.

Table 14: Summary of Key Model Parameters

Parameter	Sponsor's estimate
Target population	
Patients taking an ICS-LABA whose asthma remains uncontrolled	53%
Patients taking an ICS-LABA who receive a concomitant LAMA	[redacted]
Number of patients eligible for the drug under review (year 1/year 2/year 3)[a]	
Taking a concomitant LAMA (eligible population 1)[b]	
Medium dose	[redacted]
High dose	[redacted]
Taking an ICS-LABA only (eligible population 2)	
Medium dose	[redacted]
High dose	[redacted]
Market uptake (3 years)	
Uptake (reference scenario)	
QVM (year 1/year 2/year 3)	0%/0%/0%
Comparators	Jurisdiction-specific[c]
Uptake (new drug scenario)[d]	
Taking a concomitant LAMA (eligible population 1)	
QVM (year 1/year 2/year 3)	20%/45%/58%
Comparators	Jurisdiction-specific[e]

Parameter	Sponsor's estimate
ICS-LABA only (eligible population 2)	
QVM (year 1/year 2/year 3)	5%/17%/25%
Comparators	Jurisdiction-specific[e]
Cost of treatment (per patient)	
Cost of annual treatment	
QVM	$1,250.96
Comparators	Jurisdiction-specific

ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; LAMA = long-acting muscarinic antagonist; QVM = indacaterol acetate-glycopyrronium bromide-mometasone furoate.

[a] Summed across jurisdictions. Number of patients was based on the number of forecasted units per year, divided by the number of units per year per patient.

[b] Considered only in provinces where Spiriva Respimat (tiotropium) is not restricted to the treatment of chronic obstructive pulmonary disease (Alberta, Manitoba, NIHB, Ontario, Yukon).

[c] Projected market uptake for each ICS-LABA comparator in the reference scenario was based on jurisdiction-specific historic claims data.

[d] Uptake of QVM was assumed to be equal in the medium- and high-dose market segments.

[e] QVM was assumed to have the same impact on all current available treatment (same displacement).

Summary of the Sponsor's Budget Impact Results

Results of the sponsor's base case estimated that the reimbursement of QVM as a maintenance treatment of uncontrolled asthma will generate cost savings (expected savings: $1,265,447 in year 1; $3,280,319 in year 2; and $4,353,302 in year 3). Reimbursing QVM was estimated by the sponsor to save $8,899,068 over the 3-year period.

In each of the sponsor's scenario analyses, QVM was cost-saving, with savings ranging from $3,225,460 to $9,906,510 over 3 years.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Uncertainty regarding the number of patients eligible to receive QVM.** In deriving the target population, the sponsor assumed that 53% of patients taking an ICS-LABA would remain uncontrolled and thus be eligible for LAMA treatment. This estimate was based on a 2004 survey[22] of Canadian patients and physicians; the survey's response rate was approximately 7%, indicating a high risk of selection bias. Of those included in the study, 53% were diagnosed with uncontrolled asthma according to the 1999 Canadian Asthma Consensus Guidelines. A 2017 position statement by the Canadian Thoracic Society further differentiates between "uncontrolled" and severe asthma.[23] Uncontrolled asthma is commonly associated with nonadherence and poor inhaler technique, while severe asthma is uncommon, affecting approximately 5% of all asthma patients.[23]
  - Given the number of patients who are eligible for QVM is uncertain, this could have a significant impact on the size of the budget savings from introducing QVM.
- **Uncertainty about the indication for prescription claims.** The sponsor adopted a claims-based approach to estimating the number of patients eligible for treatment. Because claims do not provide information about the indication, for some comparators, it is unclear what proportion of claims were for asthma treatment. Multiple comparators are indicated for both asthma and COPD (i.e., Advair Diskus, Symbicort, Breo Ellipta). The

sponsor estimated the percentage of claims for asthma (versus COPD) by use of IQVIA Rx Dynamics; however, CADTH was unable to verify these estimates. The clinical expert consulted by CADTH indicated that the sponsor's estimates of the percentage of units used in the treatment of asthma were likely underestimated. Further, for drugs or strengths that are labelled or reimbursed only for asthma, all units were assumed to be used in the treatment of asthma (i.e., off-label use was not addressed).

  - The sponsor provided a scenario analysis in which all units were assumed to be used in asthma. This resulted in 20% higher total sales for QVM, resulting in 8% lower cost savings relative to the base case (−$8,156,592 versus −$8,999,068). A more accurate breakdown of COPD versus asthma claims would be needed to determine the true size of the budget savings.

- **Uncertainty about the uptake of QVM among incident versus prevalent ICS-LABA + LAMA users.** The sponsor assumed differential uptake of QVM based on whether patients were concomitantly taking a LAMA (prevalent users; eligible population 1) or were initiating LAMA for the first time (incident users; eligible population 2). The sponsor assumed that [redacted] of asthmatic patients taking an ICS-LABA would be taking a concomitant LAMA, on the basis of data from IQVIA Rx Dynamics; however, CADTH was unable to verify the validity of this estimate. The estimated uptake among these patients is anticipated by the sponsor to be 20% in year 1, 45% in year 2, and 58% in year 3. Among the remaining [redacted] of patients (new LAMA users), uptake was assumed to be 5% in year 1, 17% in year 2, and 25% in year 3. In both groups of users, the sponsor assumed that QVM would have the same uptake in the medium- and high-dose market segments. The magnitude of the QVM uptake was based on the sponsor's internal assumption and could not be verified by CADTH. The clinical expert consulted by CADTH indicated that the projected uptake in both groups is uncertain but likely overestimated. The validity of the assumption of equal displacement of currently available treatments is similarly uncertain.

- In establishing the eligible populations, the sponsor further assumed that prevalent ICS-LABA + LAMA users (eligible population 1) would be relevant only in jurisdictions where Spiriva Respimat (tiotropium) is not restricted to COPD. The sponsor considered these to be Alberta, Manitoba, Non-Insured Health Benefits, Ontario, and Yukon. Not included in the sponsor's model was British Columbia, where use is currently not restricted by indication.

  - Further data would be needed to support claims of how many asthma patients currently receive a LAMA as well as how many require a LAMA each year.

- **Uncertainty about the market share of comparator treatments.** The sponsor's submission was divided into 2 market segments (medium- and high-dose) for ICS-LABA treatments on the basis of a recommended dosing schedule from a previous CADTH pharmacoeconomic review.[21] For some comparator treatments, the same dosage can be used in 2 different market segments, depending on the number of inhalations per day (i.e., Symbicort 200/6). The sponsor assumed that the distinction between market segments would be similar to that for other comparators. To divide the claims for Symbicort 200 mcg/6 mcg between medium- and high-market segments, the sponsor assumed that the distribution of claims would be equivalent to that for the 2 doses of Breo Ellipta (100 mcg/25 mcg, 200 mcg/25 mcg). This split varied by jurisdiction. CADTH was unable to verify whether these assumptions are reasonable.

  - Further data would be needed to support claims of the breakdown of how many inhalers (for example, Symbicort) are used for medium doses versus high doses.

- **Inappropriate comparator drug costs.** While the sponsor's submission states that the generic cost was incorporated in the BIA in provinces where a generic version is available, CADTH identified several discrepancies between the sponsor's submission and provincial drug formularies. For example, in British Columbia, the price of Advair Diskus 500 mcg/50 mcg was included in the sponsor's model as $2.0417 per unit, while

the amount covered by British Columbia PharmaCare is $1.2971 per unit. This discrepancy may be due, at least in part, to changing drug prices on the provincial formularies over time. Further, the sponsor assumed that high-dose Symbicort Turbuhaler (200 mcg/6 mcg) would be administered as 4 inhalations twice daily. The clinical expert consulted by CADTH indicated that few patients would be prescribed this dosage and that this regimen would be used only to provide rapid symptom relief. High-dose Symbicort would typically be prescribed as 2 inhalations twice daily.

- The cost of some comparators was thus overestimated, leading to a potential overestimation of the savings with reimbursement of QVM.
  - Any BIA reanalysis would need to incorporate the most up-to-date costs.

CADTH Reanalyses of the BIA

CADTH did not undertake reanalysis of the sponsor's BIA. Treatment with QVM at the submitted price is less expensive compared to other ICS-LABA + LAMA comparators (Table 7 and Table 8) and will likely be cost-saving. Owing to the limitations described above, the extent of the cost savings to the drug plans is uncertain.

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